REMARKS

Claims

Claims 30–40 are pending with claims 1–29, 31 and 32 canceled without prejudice or disclaimer. Claim 41 is added by this paper.

Claim amendments

New claim 41 is supported by the disclosure contained in, for example, page 35, lines 25–28 of the originally-filed specification. See also, a definition thereof in the paragraph bridging pages 34 and 35 of the present specification. No new matter is added.

Rejections under 35 U.S.C. §112, ¶1

Claim 30 has been amended as per the Examiner's suggestion, rendering the rejection thereof moot. No agreement is to be implied. Moreover, the amendment does not narrow the scope of the claimed subject matter. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103

Claim 30, 33–38 and 40 are rejected under this section as allegedly being unpatentable over Ye (*Oncogene*, 1999), Mendelsohn (*Oncogene*, 2000) in view of Bending (US 5,558,864). This rejection is respectfully traversed.

As stated in the paragraph bridging pages 3 and 4 of the present Office Action, Ye teaches pharmaceutical compositions comprising mAb c225 (which binds to ErbB1) and mAb 4D5 (which binds to ErbB2) and guides one of ordinary skill in the art to combine c225 with 4D5 "in order to inhibit the proliferation of cancer cells stimulated by both EGF receptor and Her2 signals…and to prevent formation of active receptor heterodimers such as ErbB1/ErbB2." Ye does not teach or suggest "a pharmaceutical composition comprising a first antibody molecule or a portion thereof and a second antibody molecule or a portion thereof, having the capability to bind to different epitopes located on an ErbB1 receptor molecule (emphasis added)." Mendelsohn does nothing to add to Ye's disclosure other than to teach that the aforementioned mAb c225 can be formulated into pharmaceutical compositions comprising cytotoxic agents and the like. As expressly conceded in the first complete paragraph at page 4 of the Office Action, the claimed invention differs from the disclosures in the above-cited references because "the humanized monoclonal antibody is mAb h425 that binds to a different epitope on the ErbB1 receptor instead of mAb 4D5 that binds to ErbB2."

The Office Action then proceeds to allege that the limitations of art references can be rectified by Bendig's disclosure of humanized monoclonal antibody mAb h425 and compositions based thereon. While Bendig may teach or suggest antibody preparations of h425 containing IFNγ and TNF-α or the like; however, the reference is absolutely silent with respect to preparations comprising another antibody molecule which binds to a different epitope located on an ErbB1. Absent such teaching, a showing of *prima facie* obviousness cannot be made. The cited references do not teach or suggest all of the elements of the claims. For example, there is no showing of a second antibody molecule or a portion thereof having the capability to bind to different epitopes located on the ErbB1 receptor" or "increase in the amount of antibody bound per receptor and per cell by the same antibody dose," as presently claimed.

The basis for this rejection is further outlined in the paragraph bridging pages 7 and 8 of the Office Action, wherein the Examiner relies on the decision in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007) to allege that mAb h425 and mAb 4D5 constitute "simple substitutions" of one another. Applicants respectfully disagree with this contention. It is not clear how the PTO has arrived at the conclusion that antibodies which bind to structurally and functionally different epitopes are "simple substitutions." Absent scientific evidence to support this contention, the rejection is without merit. In any event, such mere picking of a specific molecule from the vast number of potential molecules that are available to any skilled worker is not a proper basis for establishing obviousness. For example, as disclosed in the Wikipedia reference article (submitted in Exhibit A), four different EGFR family members were known in the art. None of the above-cited references teach or suggest substituting the anti-Her2 mAb 4D5 antibody of Ye with another antibody which binds to a receptor from this family (for instance, Her-3, Her-4), let alone an antibody which is different from mAb c225 and which binds to a different epitope on the same ErbB1 receptor. As such, the rejection is without merit. There is no teaching or suggestion to select the anti-ErbB1 h425 from a list of antibodies. See, *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007), wherein the lower court held, which was upheld by the Federal Circuit, that any "suggestion to select" the molecule of interest was negated by the separate prior art document testing various prior art molecules. The Federal Circuit rejected arguments relying on *KSR* that "the claimed compounds would have been obvious because the prior art compound fell within 'the objective reach of the claims.'" Thus, it is clear that the law requires "suggestion to select" the molecules of interest from the prior art, and it is not adequate that a molecule merely fall within the objective reach of a claim. Since the suggestion to select is not provided by any of the cited references, the rejection is without legal merit.

The Federal Circuit in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd. et al.*, 87 USPQ2d 1452 (Fed.

Cir. 2008) characterized the holding of *Takeda* by stating that "obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound." Emphasis added.

The court went on to summarize the state of the law of obviousness, especially as it pertains to chemical and biological arts, as follows:

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might **identify a problem and pursue potential solutions**. Second, KSR presupposes that the record up to the time of invention would **give some reasons, available within the knowledge of one of skill in the art, to make PARTICULAR MODIFICATIONS to achieve the claimed compound.** See Takeda, 492, F.3d at 1357 ("Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a PARTICULAR MANNER to establish prima facie obviousness*** of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would **supply some reasons for narrowing the prior art universe to a "FINITE NUMBER OF IDENTIFIED, PREDICTABLE SOLUTIONS**," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that **this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable**. (Emphasis added.)

Assuming a starting reference is the article by Ye, it remains necessary to identify some reason that could have led one of ordinary skill in the art to replace the ErbB2 binding molecule (mAb 4D5) with an antibody that binds to a second different epitope on the ErbB1 receptor molecule. Absent such, under controlling law, this rejection cannot stand.

The Office Action further relies on *In re Kerkhoven* 205 USPQ 1069(CCPA 1980) to contend that "the combined use of two antibodies in pharmaceutical composition is expected to inhibit tumor growth effectively than either antibody alone given that each antibody binds to different epitope on ErbB1 receptor and each antibody has been shown to inhibit tumor growth." See, the concluding sentence in page 8, ¶1 of the open Office Action. This assertion and the rejection based thereon are both misplaced. At most, the references may teach or suggest the use of two antibody molecules each of which binding to epitopes located on two different receptors (i.e., ErbB1 and ErbB2, which are art-recognized to be different receptors) none of the references teach or suggest compositions comprising antibody

molecules which bind to different epitopes on the same ErbB1 receptor, as claimed herein. The claimed unexpected properties (i.e., causing an enhanced ErbB1 blocking and/or inhibition and induction of down-regulation of ErbB1 receptor-specific pathway signaling as compared with a composition comprising said first or second antibody molecule only) cannot be ascribed from any of the above-cited references or a combination thereof. As such, the obviousness rejection based on a combination of the aforementioned references is without legal merit.

Although not necessary to overcome the baseless obviousness rejection, Applicants' specification, at page 8, lines 24–27 expressly teaches that "the combinations according to the inventions show an astonishing synergetic effect" with respect to observation of real tumor shrinking and disintegration and without detection of significant adverse drug reactions. Experimental evidence for this statement is provided in Examples 1–5 at pages 41–44 of the instant specification. See, also the disclosure contained in Figs. 1–5 and the description thereof at page 41 of the specification. Further corroboration of the unexpected effects of cetuximab and matuzumab is provided in the scientific article by Dechant et al. (*Cancer Research*, 2008).

Therefore, it is respectfully submitted that the instantly claimed subject matter is fully inventive over the cited references and that the Office Action has failed to meet the basic criteria for *prima facie* case of obviousness. Even if the art references that are presently cited supported a finding of *prima* facie obviousness, such a finding would be overcome by the unexpected synergistic results which are obtained. As such, all the rejections under 35 U.S.C. §103(a) must be withdrawn.

Claim 39 is rejected under §103(a) as allegedly being unpatentable over the above-cited Ye, Mendehlson and Bendig references further in view of US patent no. 6,342,219 to Thorpe et al. Applicants respectfully traverse the rejection.

At the outset it is submitted that the rejection is moot in view of the aforementioned remarks and arguments, i.e., independent claim 30 is both novel and inventive over the cited primary and secondary references and the disclosure in Thorpe fails to rectify the deficiencies in the Ye, Mendelsohn and Bendig references. As such, the kits of the present invention are also unobvious over the cited references. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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